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CLINICAL STUDIES

Long-Term Variation in Myocardial Ischemia During Daily Life in Patients With Stable Coronary Artery Disease: Its Relation to Changes In the Ischemic Threshold

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Long-term variation in the frequency of myocardial ischemia during daily activity in patients with coronary artery disease who do not experience symptomatic changes has not been documented. Because at one point in time, the magnitude of such ischemia is strongly related to the ischemic threshold measured during exercise testing, this study was undertaken to determine whether patients with stable coronary artery disease show long-term variations in the frequency and duration of myocardial ischemia and to establish whether such variability is related to parallel changes in the ischemic threshold during exercise testing.

Forty consecutive patients (mean age 61 ± 8 years) who showed a stable clinical course over ≥12 months were studied with a repeat exercise treadmill test and ambulatory electrocardiographic (ECG) monitoring after withdrawal of antianginal medications. The ischemic threshold was determined as the exercise time at 1 mm of ST segment depression. The mean interval to both follow-up evaluations was 15 ± 3 months. Among the 23 patients with myocardial ischemia on ambulatory ECG monitoring at initial evaluation, the number and duration of ischemic episodes at follow-up were increased in 5 patients (mean increase 3.6 ± 2 episodes and 123 ± 98 min), unchanged in 1 patient and decreased in 17 patients (mean decrease 2.6 ± 2 episodes and 98 ± 72 min). Of the 17 patients without ischemic episodes at initial evaluation, 3 had evidence of ischemia on follow-up ambulatory ECG monitoring.

During follow-up exercise testing, the exercise ischemic threshold decreased significantly (from 12.5 ± 6 to 8 ± 4 min; $p < 0.001$) in those patients in whom the frequency (and duration) of myocardial ischemia on ambulatory monitoring increased. Conversely, the ischemic threshold significantly increased (from 8 ± 5 to 10.2 ± 5 min; $p < 0.001$) in those patients in whom the number (and duration) of ischemic episodes decreased during follow-up. The variations in the frequency of myocardial ischemia during follow-up ambulatory monitoring significantly correlated with the changes in exercise ischemic threshold ($r = -0.62$; $p < 0.0001$).

These findings indicate that patients with coronary artery disease may show long-term variations in myocardial ischemia during daily activity, even without simultaneous symptomatic changes. The occurrence and magnitude of this variation are closely related to parallel changes in the exercise ischemic threshold. These findings may have important implications for the understanding of the mechanisms and prevalence of ischemia during daily activity and the longitudinal evaluation of patients with stable coronary artery disease.

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Patients with stable coronary artery disease often experience episodes of myocardial ischemia during daily life. Most of these episodes are silent (1–3) and detection of their presence on ambulatory electrocardiographic (ECG) monitoring is believed by some (4–6) to constitute an independent indicator of prognosis. However, variations in the magnitude of such myocardial ischemia over long periods of time in patients with chronic stable ischemic heart disease have not been documented. Such data are particularly important for the clinical evaluation of patients with stable coronary artery disease. Because the prognosis of these patients is related to the presence of myocardial ischemia and not to its symptomatic manifestations (7–11), such variations over time may identify patients who have entered a different prognostic subgroup, even without the occurrence of symptomatic changes.

At one point in time, the number and duration of episodes of myocardial ischemia during daily life are closely related to the ischemic threshold measured during exercise testing (12–15). We therefore hypothesized that individual variations in the magnitude of myocardial ischemia over time would be reflected by changes in the exercise ischemic threshold. If this relation exists, it would provide a better understanding of the nature of long-term variation in myocardial ischemia in patients with stable coronary artery

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disease; it would also allow the prediction of changes in the magnitude of ischemia from the analysis of serially performed exercise tests.

The purpose of this study was therefore twofold: 1) to determine whether patients with coronary artery disease who do not experience changes in symptomatic status show variations in the frequency and duration of myocardial ischemia experienced in daily living during long-term evaluation, and 2) to establish whether the occurrence of such variation can be accounted for by changes in the exercise ischemic threshold during the same period of observation.

Methods

Selection of patients. Forty consecutive patients were retrospectively selected for this study because they met the following criteria: 1) angiographically proved coronary artery disease (that is, ≥70% narrowing in one or more major coronary vessels); 2) longitudinal evaluation of ≥12 months' duration; 3) stable clinical course without changes in symptoms, acute myocardial infarction, unstable angina or coronary revascularization; and 4) exercise treadmill test and ambulatory ECG monitoring data of sufficient technical quality to assess reliably the ischemic threshold and number and duration of episodes of myocardial ischemia at initial and most recent evaluations. This serial noninvasive evaluation is routinely performed in patients with coronary artery disease at our institution at approximately annual intervals, regardless of the changes in symptoms or the occurrence of unpredictable events that patients may experience during the follow-up period.

There were 28 men and 12 women with a mean age of 61 ± 8 years (range 38 to 75). All patients were in New York Heart Association functional class I or II. Twenty-two patients were asymptomatic and 18 had only mild symptoms. Twelve of the 40 study patients had a history of documented myocardial infarction, but no infarction occurred in the 3 months before the study. Thirty-six of the 40 study patients received antianginal medications during the study period, including a beta-adrenergic blocking agent in 28, a calcium channel blocking agent in 18 and a long-term nitrate in 10. Twenty-one patients were being treated with one drug and 15 with two or three drugs. Medical therapy in each patient was not altered during the study period and therefore was the same before the tests performed at both the initial and most recent evaluation.

Seventeen patients (42%) had single-vessel disease, 14 (35%) had double-vessel disease and the remaining 9 (23%) had involvement of all three major coronary vessels. Left ventricular function was assessed with radionuclide ventriculography (16). At the initial evaluation, left ventricular ejection fraction at rest for the overall study group was 52 ± 12% (range 28 to 70%) and was considered to be normal (≥45%) (17) in 29 of the 40 study patients.

Twenty-five patients had a normal rest ECG, 10 had abnormal Q waves compatible with old myocardial infarction and the remaining 5 had minor ECG abnormalities, including incomplete right bundle branch block in 2, first degree atrioventricular block in 2 and left axis deviation in 1 patient. No patient had repolarization abnormalities on the rest ECG. In particular, patients with left bundle branch block, those taking digitalis and those with ECG signs of left ventricular hypertrophy were excluded from the study.

After informed consent was obtained, patients underwent a treadmill exercise test, followed by one period of ambulatory ECG monitoring at each evaluation. All studies were performed after withdrawal of antianginal medications for ≥48 h. During ambulatory monitoring, patients took sublingual nitroglycerin for chest pain, but prophylactic administration was not allowed. The mean interval between the initial and most recent evaluation was 15 ± 3 months (range 12 to 24).

Ambulatory ECG monitoring. Patients underwent a 48-h period of ambulatory ECG monitoring at each evaluation. After careful skin preparation, electrodes were placed to record lead CM_5 and modified lead II (12). Patients were encouraged to carry out their normal daily activities during the 48-h period of monitoring and were instructed to keep a detailed diary of their activities, symptoms and consumption of sublingual nitroglycerin. Tapes were analyzed by an independent reader at 60 to 120 times normal speed, utilizing a Del Mar Avionics model 750A system. Printouts at a paper speed of 25 mm/s were obtained before, during and after any change in the ST segment level. An ischemic episode was defined as ≥1-mm ST segment depression at 0.08 s after the J point, lasting for ≥1 min. Return of the ST segment level to baseline for ≥3 min was required between two episodes. Changes in the configuration of the T wave without simultaneous shifts in the ST segment were not considered evidence of ischemia. The magnitude of myocardial ischemia was determined for each patient at the initial and most recent evaluation as the number and total duration of ischemic episodes during each 48-h monitoring period.

Exercise testing. Treadmill exercise tests were performed with use of the National Institutes of Health combined protocol (15,18). This exercise protocol employs slow increases in work load, thus allowing accurate estimation of the ischemic threshold that closely correlates with the results of ambulatory monitoring (15). The protocol has also proved to be useful for the serial noninvasive evaluation of patients with coronary artery disease (18).

Patients exercised until one of the following developed: chest pain, ST segment depression ≥4 mm, decrease in systolic blood pressure ≥20 mm Hg, ventricular tachycardia, extreme fatigue or shortness of breath. Twelve-lead ECGs were routinely obtained at rest, at every minute during exercise and at peak exercise. In addition, the ECG was constantly assessed throughout the test directly from the monitor, utilizing leads II, aVF and V_5. Printouts were obtained whenever repolarization changes were observed.

This procedure allowed detection of ST segment changes at 0.5-minute intervals in some patients. Tests were considered positive when planar or downsloping ST segment depression ≥1 mm at 0.08 s after the J point was observed during exercise.

The ischemic threshold was determined at the initial and most recent evaluation as the time of exercise at which 1 mm of ST segment depression developed. We (15) have shown that this measurement of the ischemic threshold correlates closely with the number and duration of ischemic episodes during ambulatory ECG monitoring when it is obtained with an exercise protocol that produces slow increases in work load (such as the National Institutes of Health combined protocol).

Statistical analysis. Mean values on exercise testing and ambulatory ECG monitoring were compared with use of the paired *t* test. Proportions were compared by chi-square analysis. Relations among variables were assessed by means of Pearson's correlation coefficient. All reported p values are two-tailed. A p value <0.05 was considered significant.

Results

Ambulatory ECG monitoring (Table 1). At initial evaluation, 23 patients (57%) had at least one episode of ST segment depression during ambulatory ECG monitoring. A total of 132 ischemic episodes were recorded, 87% of which were silent. The average number of ischemic episodes/patient over the 48-h recording period was 3.3 (range 0 to 18). The total duration of these episodes was 3,332 min (75% were silent), with a mean of 83 min (range 0 to 580)/patient.

Of the 23 patients with evidence of myocardial ischemia at initial ambulatory ECG evaluation, 5 showed an increase in the number and duration of episodes at follow-up (mean increase 3.6 ± 2 episodes [range 2 to 7] and 123 ± 98 min [range 13 to 330]); 1 patient showed no change and the remaining 17 patients had a decrease in the number and duration of ischemic episodes (mean decrease 2.6 ± 2 episodes [range 1 to 9] and 98 ± 72 min [range 11 to 363]) including 4 patients in whom no episodes were recorded at the most recent evaluation (Table 1).

Of the 17 patients without episodes of myocardial ischemia during monitoring at their initial evaluation, 3 developed evidence of ischemia on follow-up, including 2 with two ischemic episodes and 1 with three episodes.

Thus, at the most recent evaluation, 22 (55%) of the 40 patients showed ischemic episodes during ambulatory monitoring. The total number of ischemic episodes was 112, 82% of which were silent; the average number of episodes per patient was 2.8 ± 3 (range 0 to 17). The total duration of ischemic episodes was 3,357 minutes (77% were silent), with a mean duration of 84 (range 0 to 485) min/patient.

Relation of ambulatory monitoring to the exercise ischemic threshold (Table 1). At initial evaluation, 25 of the 40 patients developed ST segment depression during treadmill exercise testing; the remaining 15 had a negative stress test. Twenty-one (84%) of the 25 patients with a positive exercise test but only 2 (13%) of the 15 patients with a negative stress test had episodes of myocardial ischemia during monitoring ($p < 0.0001$).

At both the initial and most recent evaluations, there was a strong inverse correlation between the ischemic threshold measured at exercise testing and the frequency of ischemic episodes during ambulatory monitoring (Fig. 1). A significant correlation was also observed between the ischemic threshold and the total duration of ischemia at both the initial and the most recent evaluation ($r = -0.45$ and $r = -0.48$, respectively; $p < 0.03$). Thus, patients in whom 1 mm of ST segment depression developed early during the exercise test (low ischemic threshold) had several ischemic episodes and a prolonged duration of ischemia during monitoring; conversely, patients in whom 1 mm of ST segment depression did not occur or occurred during the later stages of the test (high ischemic threshold) had few or no episodes and a shorter duration of ischemia during monitoring.

The exercise ischemic threshold decreased significantly (shortening of the time of exercise at 1 mm of ST segment depression) from 12.5 ± 6 min at initial evaluation to 8 ± 4 min at the most recent evaluation ($p < 0.001$) in those patients in whom the frequency (and duration) of myocardial ischemia increased during follow-up ambulatory monitoring. Conversely, the ischemic threshold (the time of exercise to 1 mm of ST segment depression) significantly increased from 8 ± 5 to 10.2 ± 5 min ($p < 0.001$) in those patients in whom the number and duration of ischemic episodes decreased during follow-up ambulatory monitoring (Fig. 2).

Of the three patients who did not have evidence of ischemia at initial ambulatory ECG evaluation but showed ischemic episodes on follow-up monitoring, two had a substantial reduction in the exercise ischemic threshold and the remaining patient had a negative stress test result initially that became positive at the most recent evaluation. Most important, for the 25 patients whose ischemic threshold could be measured (that is, they developed ST segment depression during exercise testing), the variations in the frequency of myocardial ischemia during follow-up ambulatory ECG monitoring strongly correlated with the changes in exercise ischemic threshold (Fig. 3).

Repeat cardiac catheterization. Of the eight patients who showed an increase in the frequency and duration of myocardial ischemia on ambulatory ECG monitoring (and a decrease in the exercise ischemic threshold) during follow-up testing, five also showed a simultaneous worsening in the ejection fraction response to exercise assessed by radionuclide angiography without significant changes in symptoms. These five patients had been previously found to have double-vessel (three patients) or triple-vessel (two patients) coronary artery disease. Because of these constellation of findings, these five patients underwent repeat coronary angiography. The time interval between the two angiograms was 1 to 8 years (mean 3). Each of the five patients showed

Table 1. Ischemic Threshold (exercise time to 1 mm of ST segment depression) and Number of Ischemic Episodes During Ambulatory Electrocardiographic Monitoring at the Initial (I) and the Most Recent (II) Evaluation in the 40 Study Patients With Stable Coronary Artery Disease

Pt No.	Age (yr)/ Gender	Ischemic Threshold (min)			No. of Episodes		
		I	II	Change	I	II	Change
1	69/M	—	—	—	0	0	—
2	68/M	—	—	—	0	0	—
3	49/F	7	11.5	↑	6	0	↓
4	65/F	—	—	—	0	0	—
5	70/M	2.5	5	↑	8	4	↓
6	63/M	—	—	—	0	0	—
7	52/M	—	—	—	0	0	—
8	75/M	12.5	15	↑	2	1	↓
9	58/F	17.5	13	↓	1	4	↑
10	57/M	12.5	8.5	↓	1	5	↑
11	67/F	2	6	↑	12	3	↓
12	64/M	2.5	2.5	—	2	2	—
13	61/F	8.5	12	↑	6	4	↓
14	62/F	8	2.5	↓	8	4	↓
15	65/M	1.5	2.5	↑	18	17	↓
16	57/M	3.5	9.5	↑	10	4	↓
17	67/M	3.5	2.5	↓	6	8	↑
18	56/F	—	—	—	1	0	↓
19	57/M	—	—	—	0	0	—
20	46/F	—	—	—	0	0	—
21	48/M	—	9.5	↓	0	3	↑
22	38/M	—	—	—	0	0	—
23	52/M	—	—	—	0	0	—
24	50/M	17.5	11	↓	0	2	↑
25	67/F	1	2.5	↑	13	12	↓
26	71/M	15	11	↓	0	2	↑
27	71/M	17.5	18.5	↑	7	6	↓
28	49/M	2.5	2	↓	4	11	↑
29	74/M	—	—	—	0	0	—
30	60/F	—	—	—	0	0	—
31	67/M	13.5	12.5	↓	7	9	↑
32	59/M	—	—	—	1	0	↓
33	64/F	6	7.5	↑	3	2	↓
34	60/M	17.5	19	↑	0	0	—
35	60/M	9.5	12	↑	6	4	↓
36	66/M	—	15	↓	0	0	—
37	67/F	8	5	↓	0	0	—
38	52/M	17	18.5	↑	1	0	↓
39	63/M	4.5	7	↑	6	3	↓
40	66/M	19.5	20	↑	3	2	↓

F = female; M = male; Pt = patient; ↑ = increase in ischemic threshold (prolongation in time of exercise to development of 1 mm of ST segment depression) or number of ischemic episodes; ↓ = decrease in ischemic threshold (reduction in time of exercise to development of 1 mm of ST segment depression) or number of ischemic episodes.

angiographic evidence of disease progression: all three patients who initially had shown double-vessel disease had triple-vessel coronary artery disease; the two patients who initially had triple-vessel disease showed complete occlusion of a previously partially stenotic coronary segment. Coronary revascularization was recommended for all these patients on the basis of triple-vessel coronary artery disease and evidence of inducible myocardial ischemia despite the lack of significant symptoms (10,11). Three patients subsequently underwent coronary artery bypass graft surgery, one had percutaneous balloon angioplasty and the remaining patient refused an operation.

Discussion

Correlation of ischemic episodes during ambulatory ECG monitoring with exercise ischemic threshold. The frequency of episodes of myocardial ischemia that patients with coronary artery disease often experience during ambulatory ECG monitoring may show circadian and short-term variation, as reported in previous studies (12,19–23). The results of the present investigation demonstrate that a substantial variation in the number and duration of these episodes may also be observed over long-term intervals in patients who manifest a symptomatically stable clinical course. Furthermore, our findings indicate that this long-term variation correlates with changes in the ischemic threshold (as measured from exercise testing) that occur during the same interval. Thus, the frequency and total duration of ischemic episodes during ambulatory monitoring decrease in those patients with an increase in the exercise ischemic threshold (prolongation in the time of exercise at the occurrence of repolarization changes) during follow-up testing. Conversely, the number and duration of ischemic episodes increase in those patients with a decrease in the ischemic threshold (reduction in the time of exercise at the development of ECG changes) during follow-up study.

The results of this study confirm previous reports (12–15) indicating that the number and duration of episodes of myocardial ischemia during daily life closely correlate with the results of exercise testing and they expand those observations by demonstrating that variations in the magnitude of myocardial ischemia during serial ambulatory ECG evaluations reflect changes in the exercise ischemic threshold. Hence, the long-term variation in myocardial ischemia during daily activity can be largely predicted by analysis of serially performed exercise tests. The observation that the magnitude of changes in the frequency and duration of episodes of ischemia detected on ambulatory ECG monitoring significantly correlated with the magnitude of changes in the exercise ischemic threshold indicates that such variation in myocardial ischemia during daily life cannot be solely ascribed to spontaneous variability inherent in ambulatory ECG monitoring (22,23).

Mechanisms and clinical significance of silent ischemia. The identification of this parallel long-term variation in the frequency and duration of episodes of myocardial ischemia and exercise ischemic threshold may provide additional insights into the mechanisms and clinical significance of silent myocardial ischemia in patients with stable coronary artery disease. Because these indexes of myocardial ischemia may substantially vary without accompanying symptomatic changes, symptoms are not a reliable indicator of the

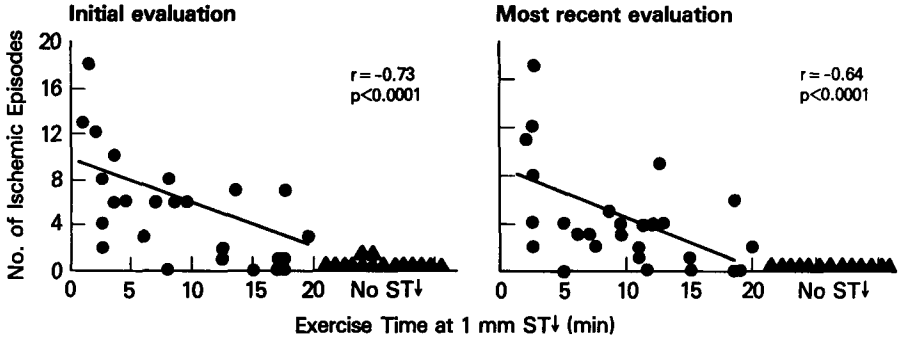


Figure 1. Correlation between ischemic threshold measured during the exercise test as the time of exercise at 1 mm of ST segment depression (ST ↓) and the number of ischemic episodes during ambulatory electrocardiographic monitoring in patients with stable coronary artery disease at initial evaluation (**left panel**) and after a mean follow-up period of 15 months (**right panel**). Patients with a positive exercise test are indicated by **circles** and those with a negative test are indicated by **triangles**. Only patients with a positive exercise test (in whom the ischemic threshold could be measured) were considered in the calculation of the correlation coefficient.

variation in the magnitude of daily myocardial ischemia or of changes in the ischemic threshold. More important, because prognosis in patients with coronary artery disease is dependent on the coronary anatomy and the magnitude of myocardial ischemia, and not on the presence or absence of ischemic symptoms (7–11), these findings emphasize the need for serial noninvasive assessment of these patients despite lack of symptomatic changes during longitudinal evaluation. For example, previous studies (10,11,24,25) in patients with triple-vessel disease have indicated that patients with inducible ischemia have a considerably worse prognosis than do those without inducible ischemia. Such results suggest that patients with triple-vessel disease and minimal or no ischemia who experience a worsening of indexes of myocardial ischemia over time (expressed as an increase in the number and duration of ischemic episodes detected on ambulatory ECG monitoring and a decrease in the exercise ischemic threshold) might benefit from coronary revascularization despite the absence of severe symptoms (10,11,24,25). In patients with single- or double-vessel disease, such changes will probably not have the same significance (25); however, further evaluation would be advisable to determine whether triple-vessel disease or left ventricular dysfunction (26) has developed.

This recommendation is further supported by our observation that worsening of the ejection fraction response to exercise, an important prognostic indicator in patients with stable coronary artery disease (10,11), occurred in five of the eight patients with an increase in the magnitude of ischemia on ambulatory ECG monitoring and a decrease in the exercise ischemic threshold during follow-up testing, even

Figure 2. Changes in ischemic threshold (time of exercise at 1 mm of ST segment depression [ST ↓]) in patients with stable coronary artery disease who showed an increase (**hatched bar**) or decrease (**solid bar**) in the frequency of myocardial ischemia detected on ambulatory electrocardiographic monitoring during follow-up testing.

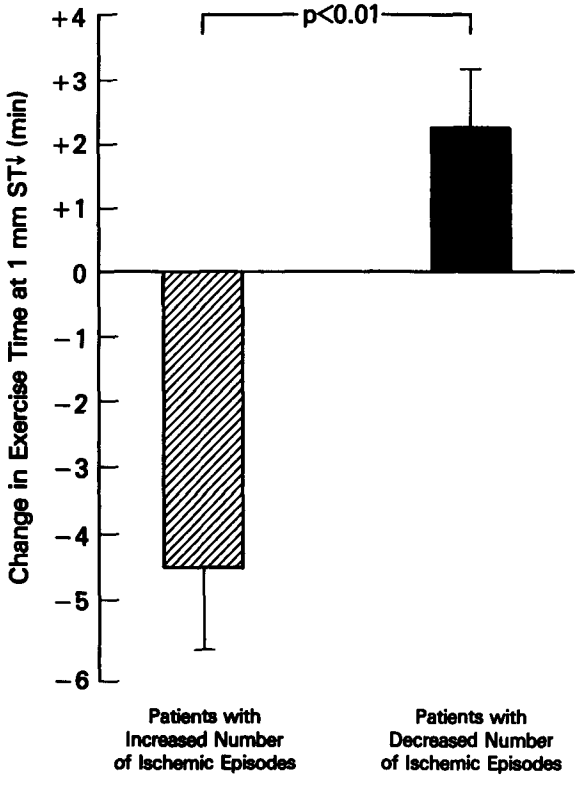
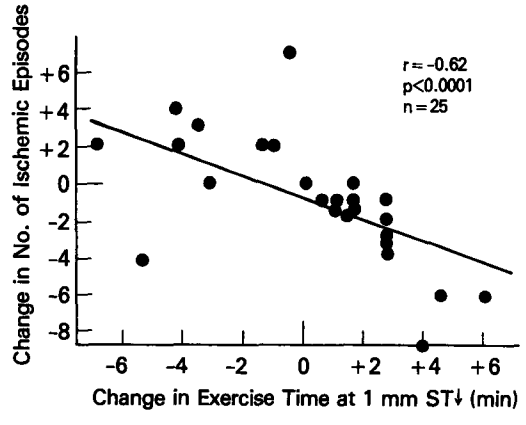


Figure 3. Correlation between changes in ischemic threshold measured during exercise testing as the time of exercise at 1 mm of ST segment depression (ST ↓) and changes in the number of ischemic episodes during ambulatory electrocardiographic monitoring in patients with stable coronary artery disease.



without simultaneous changes in symptoms. The documentation of anatomic progression in the severity of coronary artery disease and the consequent indication for coronary revascularization in these patients emphasize the clinical significance of our findings.

Mechanisms of changes in magnitude of silent ischemia. Several mechanisms may account for the changes in the magnitude of myocardial ischemia observed during long-term serial ambulatory ECG evaluation. For instance, the reduction in the frequency of these episodes or their disappearance might be secondary to regression of coronary atherosclerosis (27–29) or to the development of coronary collateral vessels (30–32). Similarly, the increase in the number of ischemic episodes might be a consequence of progression of the atherosclerotic process, with further narrowing or occlusion of the coronary vessels (28,29,33,34) as documented in five of our patients. However, because our study patients had a stable clinical course, serial coronary angiography was not routinely performed; therefore, we cannot be certain about the frequency with which variations in myocardial ischemia detected by ambulatory ECG monitoring or exercise testing will predict changes in the coronary anatomy. Finally, changes in coronary flow secondary to alterations in the coronary vasomotor tone could also be responsible for variations in the magnitude of myocardial ischemia (35,36). It is our belief that the mechanisms responsible for the long-term variation in ambulatory myocardial ischemia probably vary from patient to patient, as they undoubtedly reflect multifactorial pathophysiologic processes.

Limitations of study. Certain limitations inherent in our study design must be noted. First, our study group comprised patients with angiographically proved coronary artery disease and a symptomatically stable clinical course during the period of observation. Therefore, our results may not be applicable to other subsets of patients with ischemic heart disease, such as patients with unstable angina or recent myocardial infarction or those without significant narrowing of the epicardial vessels. Second, because the relation between the results of exercise testing and ambulatory ECG monitoring is dependent on the exercise protocol (15), the changes in the magnitude of myocardial ischemia during daily activity may not be predicted by exercise testing using protocols with faster increments in work load than we employed. Finally, because this study was not designed to determine the relation between serial changes in ischemia and the subsequent occurrence of clinical events, definitive suggestions regarding the relevance of our findings to therapeutic decisions await long-term follow-up study in a large group of patients.

Conclusions. The results of this study demonstrate that patients with coronary artery disease may experience variations in the magnitude of myocardial ischemia during daily activity over long-term intervals despite the lack of symptomatic changes during the same period of observation. The occurrence and magnitude of this variation are closely related to parallel changes in the ischemic threshold as measured during exercise testing. These findings provide insight relating to the mechanisms responsible for variations in the prevalence and duration of myocardial ischemia during daily activity and highlight an important area of future investigation: namely, the prognostic and therapeutic implications of changes in such ischemia and in ischemic threshold in patients with stable coronary artery disease.

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